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For: A METHOD OF PREVENTING PARTURIENT HYPOCALCEMIA
IN ANIMALS AND COMPOSITIONS USED THEREIN

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Sir:

Applicant respectfully submits the certified copies of Denmark Patent Applications Nos. 1999 00380, filed March 18, 1999 and 1999 01395, filed September 30, 1999, in connection with the above-identified patent application. Applicant claimed foreign priority benefits under 35 U.S.C. § 119 from the Denmark Applications in a Declaration executed on March 16, 2000, and filed in the U.S. Patent and Trademark Office on March 17, 2000.

Respectfully submitted,

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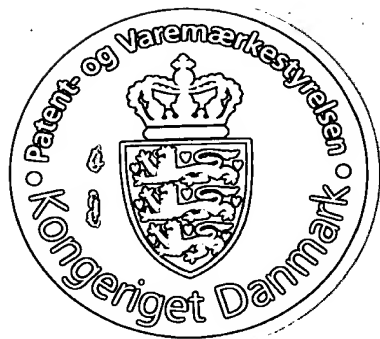
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This is to certify the correctness of the following information:

The attached photocopy is a true copy of the following document:

The specification, claims and abstract as filed with the application on the filing date indicated above.



**Patent- og
Varemærkestyrelsen**
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Ny dansk patentansøgning

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A method of preventing hypocalcemia in lactating
animals and compositions used therein

Vor ref: 22243 DK 2

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A METHOD OF PREVENTING HYPOCALCEMIA IN LACTATING ANIMALS AND COMPOSITIONS USED THEREIN

5 FIELD OF THE INVENTION

The present invention provides a method of preventing hypocalcemia in lactating animals and in particular there is provided compositions which can be administered to the animals during the dry period to prevent hypocalcemia and milk fever.

10

TECHNICAL BACKGROUND AND PRIOR ART

Hypocalcemia is a metabolic disease of lactating animals, such as dairy cows, and occurs as subclinical hypocalcemia around calving and in early lactation and in severe cases lactating animals contract clinical milk fever (parturient paresis). The lactation cycle of a dairy cow extends for approximately 10 month of the year immediately subsequent to calving. Lactation by dairy cows is at a minimum during the two month immediately prior to calving, and the dairy cows are normally not milked during this "dry period". The act of calving induces lactation in the dairy cow, and milk production is at a peak by 4-6 weeks thereafter.

During the dry period, the dairy cow has a low demand for calcium, and is thus able to absorb sufficient calcium via the digestive tract by simple passive diffusion. During lactation the demand for calcium is high, which leaves the cow in a negative calcium balance, which results in the activation of the vitamin D-dependent complex mechanisms. The lactating cow is thus capable of increasing the utilisation of the feed ration calcium by increasing absorption from the digestive tract and by resorbing calcium from the skeletal system via the blood. By these active mechanisms the lactating cow is capable of covering up to 80% of its demand for calcium during lactation (Klooster, 1976). Therefore, lactating animals are capable of preventing hypocalcemia to occur due to these powerful natural defence mechanisms almost regardless of the calcium intake via the feed.

However, during the dry period these natural defence mechanisms are deactivated, as the demand for calcium is low. Upon calving and onset of lactation there is an immediate demand for high levels of calcium to be supplied via the blood circulation to the mammary glands for milk production. The calcium regulating mechanisms are not
 5 prepared for this sudden demand for calcium in the high yielding dairy cow, and it must thus contract hypocalcemia and milk fever. Symptoms of milk fever, such as lowering of body temperature, usually become manifest within one day before and four days after calving.

10 Extensive research has been conducted to develop methods for preventing or treating milk fever. It has been observed that the risk for milk fever is reduced when the acid-base balance of the dairy cow is manipulated by acidifying dietary ration composition (Dishington, 1982). Presently, a method based on this principle is widely used in the USA. However, acidification of dairy cows is unnatural, since urine from ruminants
 15 normally is alkaline. Furthermore, overdosage has been reported.

Another approach of preventing milk fever is the peroral drenching with calcium chloride around calving (Jørgensen, 1990). The effect of this method is interpreted as a simple calcium diffusion through the wall of the forestomach and through the wall of
 20 the small intestine. However, there are several drawbacks associated with this method. The dairy cows have to be handled and dosed individually, which involves the above mentioned problems. Furthermore, the precise calving time of the cow must be known, because the first drenching is recommended to be carried out a few hours before calving.

25

Injection of a synthetic D-vitamin preparation in large doses has been suggested for the prevention and/or treatment of milk fever. Although this method is documented to be effective, it is not allowed in many countries. Another suggestion involves continuous milking, which will prevent milk fever, as the calcium regulating
 30 mechanisms are constantly activated. However, this method is only applicable to single cows which are known or suspected to contract milk fever, but it is not feasible at a herd level. Furthermore, it has been observed that the risk of milk fever can be reduced by feeding the dairy cows a dietary ration having a high calcium content prior to calving.

Ramberg et al. (1970) observed that milk fever can be controlled and/or eliminated by administering a low calcium dietary ration to dairy cows during the weeks immediately prior to calving. By feeding a low calcium dietary ration, the cow is left in a negative calcium balance, which results in the activation of its natural calcium regulating mechanisms. Unfortunately, there are many problems associated with this method. For example, most of the cattle feed, such as alfalfa and other legumes, contain too high levels of calcium to bring the dry cow in a negative calcium balance. Furthermore, the method presents a substantial problem when dealing with a large herd. To solve the above first mentioned problem, US 3,908,020 discloses a complete, calcium-limited feed ration. However, this method implies the purchase of rather expensive feed, which is not feasible under commercial dairy farming conditions, especially when the farmer is using his own grown crops for feeding.

In view of the foregoing it is evident that these currently used methods of preventing hypocalcemia involve several problems in modern farming. It is thus an important objective of the present invention to provide a novel composition and method to prevent hypocalcemia in lactating animals. The disclosed method has the advantage that its effect is based on the powerful, natural calcium regulating mechanisms of animals and at the same time it is applicable under commercial dairy farming conditions.

SUMMARY OF THE INVENTION

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Accordingly, it is the primary objectives of the present invention to provide a novel method of preventing hypocalcemia in lactating animals and a composition which is useful in such a method.

30 Thus, in a first aspect, the invention pertains to a method of preventing hypocalcemia in a lactating animal, comprising administering to the animal during at least part of the dry period an effective amount of a compound which reduces absorption of calcium from drinking water and/or from the ration of said animal.

There is also provided a composition for preventing hypocalcemia in a lactating animal, comprising an encapsulated compound which reduces the absorption of calcium from the drinking water and/or from the ration of said animal.

5 In a further aspect, the present invention relates to the use of the above composition for the prevention of hypocalcemia in a lactating animal, comprising administering to the animal during at least part of the dry period an effective amount of a compound which reduces the absorption of calcium from the drinking water and/or from the ration of the animal.

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In yet another aspect the invention pertains to a method of using the above composition for the prevention of hypocalcemia in a lactating animal, the method comprising administering to the animal during at least part of the dry period an effective amount of a compound which reduces the absorption of calcium from the
15 drinking water and/or from the ration of the animal according to the above method.

In a still further aspect, the invention relates to the use of a calcium-binding compound or a composition in the manufacturing of a medicament for preventing hypocalcemia in a lactating animal.

20

DETAILED DISCLOSURE OF THE INVENTION

It is an essential feature of the method for preventing hypocalcemia in lactating
25 animals which is provided herein that the biological effect of the compound used in the method is capable of stimulating or triggering the natural calcium regulating defence mechanism of the animal. Through this stimulating ability on the calcium metabolism before the onset of lactation, the used compound will render the animal well prepared to resist any threatening parturient hypocalcemia.

30

Thus, the method according to the invention comprises administering to the animal during at least part of the dry period an effective amount of a compound which reduces absorption of calcium from drinking water and/or from the ration of said animal. As used herein, the expression "lactating animal" designates the mammalian

class of the animal kingdom such as e.g. cow, pig, horse, cat, sheep, goat, buffalo, camels, monkey or man. Thus, the term "ration" relates both to "food" and "feed" given prior to the onset of lactation of said animal.

- 5 An advantageous feature of the method according to the invention is that the precise parturition time of the animal does not need to be known, as the compound can be given to the animal at any time during the dry period, such as at least about 1 to 4 weeks prior expected parturition, including at least about 2 to 3 weeks prior to expected parturition, and in amounts of about 10 to 1000 grams per animal per day
10 depending on the body weight of the animal.

- In presently preferred embodiments, the method according to the invention comprises administering to the animal during at least part of the dry period an effective amount of a calcium-binding compound. It will be understood that the expression "calcium-
15 binding compound" refers to compounds which are capable of binding free (ionised) calcium in aqueous solution.

- Calcium-binding compounds which are useful in the above method can be any compounds which are capable of binding free calcium in the animal gastro-intestinal
20 tract and thus trigger the natural calcium regulating defence mechanism of the animal. Such compounds include compounds that are either digestible or non-digestible in the rumen selected from the group consisting of oxalic acid, sodium oxalate, phytic acid, a phytate, a clay mineral including zeolite, sodium diethylene acetic acid, ethylenediaminetetraacetic acid (EDTA) and its sodium salts Na_2EDTA and Na_4EDTA ,
25 trisodium nitrilotriacetate monohydrate, trisodium nitriloacetate, pentasodium diethylenetriaminepentaacetate, trisodium N-hydroxyethylethylenediaminetriacetate, citric acid, a citrate, a polyphosphate, a tripolyphosphate, an orthophosphate and a cellulose phosphate and calcium-free derivatives of any such compounds.

- 30 In a presently preferred embodiment, the method according to the invention comprises administering to the animal during at least part of the dry period an effective amount of a compound which has a competitive effect on the absorption of calcium from the drinking water and/or from the ration of said animal through the wall of the gastro-intestinal tract. It is contemplated that such compounds will compete with the calcium

of the dry animal dietary ration by being preferred by the calcium absorbing mechanism. Examples of such compounds are zinc compounds including zinc oxide, ZnCl_2 and ZnSO_4 .

5 It is, as mentioned above, of considerable commercial interest to provide a method of preventing hypocalcemia in lactating animals which is applicable under commercial farming conditions. In a highly convenient embodiment of the method according to the invention, the compound used in the method is contained in a composition which is in the form of a premix, a liquid or a powder. It is contemplated that such a composition
10 can easily be administered to the dry animal perorally in a specific embodiment, be added to the drinking water and/or the ration of the dry animal.

In a further aspect of the invention there is provided a composition, which is used in the above method for preventing hypocalcemia in a lactating animal. The composition
15 comprises, in encapsulated form, a compound which reduces the absorption of calcium from the drinking water and/or from the ration of said animal.

In an advantageous embodiment of the composition according to the invention the encapsulated compound is any of the above calcium-binding compounds. It will be
20 understood that it is possible to have a mixture of two or more calcium-binding compounds in the same composition.

In one useful embodiment of the composition according to the invention, the compound has a competitive effect on the absorption of calcium from drinking water
25 and/or from the ration of the dry animal. Typical examples of such compounds are zinc compounds such as e.g. zinc oxide, ZnCl_2 or ZnSO_4 .

As mentioned above, the compounds which are used in the above compositions are encapsulated by any appropriate encapsulating material. In specific embodiments of
30 the invention, a useful compound for the encapsulation is a compound selected from the group consisting of a fat, a non-calcium derivative of a fat such as a soap and a stearate, a protein, a polysaccharide, a cellulose and a derivative of any such compound, a gum, a glycol and gelatine.

In an interesting embodiment, the composition according to the invention comprises compounds which are encapsulated by a calcium-free membran material, which at the body temperature of the lactating animal is solid at a pH value above 4.0 but which under these conditions dissolves at pH below 4.0. It is contemplated that

5 compounds encapsulated in such a membrane material can be transported through the rumen of a ruminant without being dissolved, and thus is not dissolved until it arrives in the gastrointestinal system after passage of the forestomachs of the ruminant.

In a highly convenient embodiment of the invention, the composition is in the form of
10 a premix, a liquid and a powder, or it in the form of a dragee, a tablet, a pill, or a capsule. A composition provided in such a form will be advantageous from a users point of view, since it can easily be administered to the dry animal. In a specific embodiment, the composition is added to or mixed into the drinking water and/or in the ration of the lactating animal. It is evident that such a composition is very useful,
15 when farmers use their own grown crops as feed.

In useful embodiments, the composition according to the invention is a composition comprising the above compounds and at least one further ingredient such as a vitamin, a mineral and a carrier. A useful example of such a carrier is e.g. bran.

20 Further ingredients can be selected from a sugar, a stabilising agent and a colouring agent. Additionally, the composition is calcium-free and non-acidifying, i.e. the composition is not causing biological acidification of the animal's urine.

In further aspects, the invention relates to the use of a composition according to the
25 invention, comprising administering to the animal during at least part of the dry period an effective amount of a compound which reduces the absorption of calcium from the drinking water and/or from the ration of the animal.

In a still further aspect the invention relates to the use of a composition according to
30 the present invention for the prevention of hypocalcemia in a lactating animal.

Furthermore, there is provided a method of using a composition according to the invention for the prevention of hypocalcemia in a lactating animal, the method comprising administering to the animal during at least part of the dry period an

effective amount of a compound which reduces the absorption of calcium from the drinking water and/or from the ration of the animal according to the method of the present invention.

- 5 In addition, the present invention relates to the use of a calcium-binding compound or a composition according to the invention in the manufacturing of a medicament for preventing hypocalcemia in a lactating animal.

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CLAIMS

1. A method of preventing hypocalcemia in a lactating animal, comprising administering to the animal during at least part of the dry period an effective amount of a compound which reduces absorption of calcium from the drinking water and/or from the ration of said animal.
2. A method according to claim 1, comprising administering to the animal during at least part of the dry period an effective amount of a calcium-binding compound.
3. A method according to claim 2 wherein the calcium-binding compound is selected from the group consisting of oxalic acid, sodium oxalate, phytic acid, a phytate, a clay mineral including zeolite, ethylenediaminetetraacetic acid (EDTA) and its sodium salts Na_2EDTA and Na_4EDTA , trisodium nitrilotriacetate monohydrate, trisodium nitriloacetate, pentasodium diethylenetriaminepentaacetate, trisodium N-hydroxyethylethylene-diaminetriacetate, citric acid, a citrate, a polyphosphate, a tripolyphosphate, an orthophosphate and a cellulose phosphate and a calcium-free derivative of any such compounds.
4. A method according to claim 1, comprising administering to the animal during at least part of the dry period an effective amount of a compound which has a competitive effect on the absorption of calcium from the drinking water and/or from the ration of said animal.
5. A method according to claim 4 wherein the compound is a zinc compound including zinc oxide, ZnCl_2 and ZnSO_4 .
6. A method according to claim 1 wherein the compound is contained in a composition which is in the form of a premix, a liquid and a powder.
7. A method according to claim 6 wherein the composition is added to the drinking water and/or to the ration of the dry animal.

8. A composition for preventing hypocalcemia in a lactating animal, comprising, in encapsulated form, a compound which reduces the absorption of calcium from the drinking water and/or from the ration of said animal.

5 9. A composition according to claim 8 where the compound is a calcium-binding compound.

10. A composition according to claim 9 where the calcium-binding compound is selected from the group consisting of oxalic acid, sodium oxalate, phytic acid, a
10 phytate, a clay mineral including zeolite, ethylenediaminetetraacetic acid (EDTA) and its sodium salts Na_2EDTA and Na_4EDTA , trisodium nitrilotriacetate monohydrate, trisodium nitriloacetate, pentasodium diethylenetriaminepentaacetate, trisodium N-hydroxyethyl-ethylenediaminetriacetate, citric acid, a citrate, a polyphosphate, a tripolyphosphate, an orthophosphate and a cellulose phosphate and a calcium-free
15 derivative of any such compounds.

11. A composition according to claim 8 where the compound has a competitive effect on the absorption of calcium from drinking water and/or from the ration of the animal.

20 12. A composition according to claim 11 where the compound is a zinc compound including zinc oxide, ZnCl_2 and ZnSO_4 .

13. A composition according to claim 8 where the compound is encapsulated by a compound selected from the group consisting of a fat, a non-calcium derivative of a
25 fat such as a soap and a stearate, a protein, a polysaccharide, a cellulose, a gum, a glycol, gelatine and a derivative of any such compound.

14. A composition according to claim 8 where the compound is encapsulated by a calcium-free membrane material, which at the body temperature of the lactating
30 animal is solid at a pH value above 4.0 but which dissolves at pH below 4.0.

15. A composition according to claim 8 where the composition is in the form of a premix, a liquid and a powder.

16. A composition according to claim 15 where the composition is added to the drinking water and/or to the ration of the dry animal.

17. A composition according to claim 8 where the composition comprises at least one further ingredient such as a vitamin, a mineral or a carrier.

18. A composition according to claim 8 where the composition is calcium-free and non-acidifying.

19. Use of a composition according to any of claims 8-18 for the prevention of hypocalcemia in a lactating animal, comprising administering to the animal during at least part of the dry period an effective amount of a compound which reduces the absorption of calcium from the drinking water and/or from the ration of the animal.

20. A method of using a composition according to any of claims 8-18 for the prevention of hypocalcemia in a lactating animal, the method comprising administering to the animal during at least part of the dry period an effective amount of a compound which reduces the absorption of calcium from the drinking water and/or from the ration of the animal.

20

21. Use of a calcium-binding compound or composition according to any of claims 8-18 in the manufacturing of a medicament for preventing hypocalcemia in a lactating animal.

25

ABSTRACT**A METHOD OF PREVENTING HYPOCALCEMIA IN LACTATING ANIMALS AND
COMPOSITIONS USED THEREIN**

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Method of preventing hypocalcemia and milk fever (parturient paresis) in lactating animals comprising administering to the animal during the dry period a compound which reduces absorption of calcium from the drinking water and/or from the ration of said animal. The method is based on the powerful, natural calcium regulating

10 mechanisms and is applicable under commercial farming conditions.